Claims 1-3 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner has alleged the following basis for the rejections under §112, second paragraph:

1. The language "optionally substituted" is unclear;
2. The term "heterocyclic in the definition of Ar is unclear; and
3. The scope of "alkyl," "alkenyl," etc. in claim 1 reads on carbon chains of non-limited length.

The term "optionally substituted" is clearly defined and described in the specification such that the intended meaning of the term "optionally substituted" in claims 1-3 would have been readily apparent to one skilled in the art. See, for example, the specification at page 26, line 9 to page 27, line 7 for a definition of optionally substituted.

The language "...heterocyclic groups containing one or more heteroatom(s)..." is not indefinite. As recited by the specification and as defined in the claims as filed, heterocycle inherently comprises at least one ring atom selected from N,O, and S. See, for example, page 30, line 5 to page 31, line 18 for a definition of the term "heterocyclic group" and a list of exemplary heterocyclic groups.

The scope of the terms "alkyl," "alkenyl," etc. in claim 1 is not indefinite.

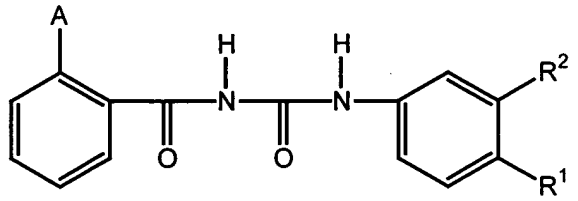
The specification clearly supports and enables the above recitation of "alkyl," "alkenyl," etc. in claim 1. See, for example, page 27, line 18 to page 31, line 23. Moreover, Applicants respectfully point out that the specification provides a number of exemplary working examples comprising a variety of linear, branched and cyclic alkyl groups.

Claims 1-6 were rejected under 35 U.S.C. 102(b) as being anticipated by Miesel et al. Chem. Abstract 96:35307 (which corresponds to U.S. Patent 4,293,552) and compounds having registry numbers 59489-79-1, 49489-82-6, and 69816-4.

The rejection is traversed.

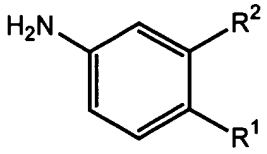
As U.S. Patent 4,293,552 and the CAPlus search printout is understood, Miesel teaches a series of pyrazinyl substituted urea compounds and precursors to making same.

More particularly, Miesel teaches compounds of the general formulae:

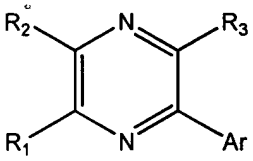


where R^1 may be, among other selections, phenyl or napthyl; and
R^2 is hydrogen, halo, methyl, ethyl, cyano, halomethyl or haloethyl;

Miesel teaches that the above urea compounds are prepared from pyrazine compounds of the formula:



In contrast the claims, as amended, of the present invention provide compounds of the formula:

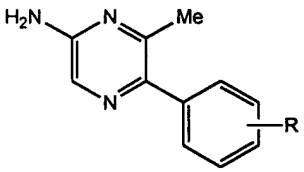


In which–NH_2 is excluded from R_2. Applicants note that the claims continue to contemplate compounds in which R_2 is an optionally substituted alkylamino. That is, compounds having one or more alkyl groups which may be optionally substituted as provided by the specification, are within the scope of the claim 1 as presently amended.

Thus claims 1 and 3 are patentable over Miesel. Claims 2 and 4-6 depend from claim 1 and are therefore also patentable over Miesel.

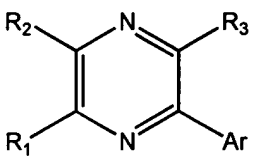
Claims 1-6 were rejected under 35 U.S.C. §102(b) as being anticipated by Barnett et al. (U.S. Patent 4,211,870).

As the reference is understood, Barnett teaches compounds of the formula:



where R is 3-trifluoromethyl, 4-chloro, or 4-ethyl

In contrast the claims, as amended, of the present invention provide compounds of the formula:



In which–NH_2 is excluded from R_2.

Thus claims 1 and 3 are patentable over Barnett. Claims 2 and 4-6 depend from claim 1 and are therefore also patentable over Barnett.

Applicants respectfully request reconsideration of claims 7-26, 30, 42-130, 133-146, 154, 155, and 162. None of the prior art relied upon by the Examiner reads upon any of claims 1-6. As provided by MPEP 803.02, reexamination of the amended Markush-type claim is proper after the claims have been amended to exclude species of a Markush group which is anticipated or rendered obvious by the prior art.

It is respectfully submitted that the subject application is in a condition for allowance. Early and favorable action is requested.

Applicants believe that additional fees are not required for consideration of the within Amendment. However, if for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105**.

Respectfully submitted,

Date: March 13, 2003 By: _____

John B. Alexander, Ph.D.
(Reg. No. 48,399)
EDWARDS & ANGELL, LLP
Dike, Bronstein, Roberts & Cushman
Intellectual Property Practice Group
P.O. Box 9169
Boston, MA 02209
Tel. (617) 523-3400

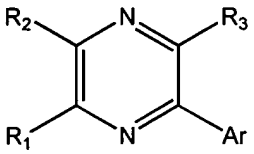
VERSION WITH CHANGES MARKED

(Additions are underlined; deletions are bracketed.)

IN THE CLAIMS

Kindly amend claims 1, 3, and 9, as follows:

1. (amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

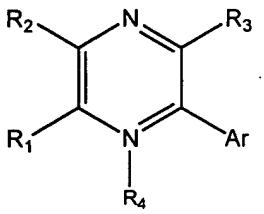
Ar is substituted phenyl, optionally substituted napthyl, or an ~~optionally-substituted heterocyclic~~ group having from 1 to 3 rings, and 3 to 8 ring members in each ring and 1 to about 3 hetero atoms;

R_1 and R_3 are each independently hydrogen, halogen, cyano, nitro, amino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted mono or dialkylamino, optionally substituted alkoxy, optionally substituted alkylthio, optionally substituted alkylsulfinyl, or optionally substituted alkylsulfonyl; and

R_2 is halogen, cyano, nitro, [amino,] optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkylamino, optionally substituted alkoxy, optionally substituted alkylthio, optionally substituted alkylsulfinyl, or optionally substituted alkylsulfonyl;

with the proviso that if Ar is phenyl substituted with halogen, napthyl, or naphthyl substituted with halogen, then the compounds where R_3 is hydrogen or amino are excluded.

3. (amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halogen, CN, C_{1-4} haloalkyl, trifluoromethyl, trifluoromethoxy, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), -O(C_{1-4} alkyl), and $S(O)_n$(C_{1-4} alkyl);

R_2 is selected from the group consisting of $-XR_A$ and Y, wherein –X, R_A, and Y are defined below and with the proviso that R_2 is not $-NH_2$; and

R_3 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, -O(C_{1-4} alkyl), -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), and -$S(O)_n$(C_{1-4} alkyl), haloalkyl, trifluoromethyl, trifluoromethoxy, $-XR_A$ and Y;

R_4 is absent or an oxygen atom;

Ar is phenyl, mono-, di-, or tri-substituted with R_C, or

Ar is selected from the group consisting of:

naphthyl, ~~pyridyl, pyridonyl, pyrimidinyl, and thiophenyl, each of which is unsubstituted or mono-, di-,~~ or tri-substituted with R_C;

with the proviso that if Ar is phenyl substituted with halogen, napthyl, or naphthyl substituted with halogen, then the compounds where R_3 is hydrogen are excluded;

R_A and R_B, which may be the same or different, are independently selected at each occurrence from the group consisting of: hydrogen and straight, branched, or cyclic alkyl groups consisting of 1 to 8 carbon atoms, which may contain one or more double or triple bonds, each of which may be further substituted with one or more substituent(s) selected from oxo, hydroxy, halogen, -O(C_{1-4} alkyl), -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), -NHC(O)(C_{1-4} alkyl), -N(C_{1-4} alkyl)C(=O)(C_{1-4} alkyl), -NHS$(O)_n$(C_{1-4} alkyl), -$S(O)_n$(C_{1-4} alkyl), -$S(O)_n$NH(C_{1-4} alkyl), -$S(O)_n$N(C_{1-4} alkyl)(C_{1-4} alkyl), and Z;

R_C is independently selected at each occurrence from the group consisting of halogen, cyano, haloalkyl, trifluoromethyl, trifluoromethoxy, hydroxy, amino, and C_{1-6} alkyl optionally substituted with 0-2 R_D, C_{2-6} alkenyl substituted with 0-2 R_D, C_{1-4} alkynyl substituted with 0-2 R_D, C_{3-7} cycloalkyl substituted with 0-2 R_D, (C_{3-7} cycloalkyl)C_{1-4} alkyl substituted with 0-2 R_D, -O(C_{1-4} alkyl) substituted with 0-2 R_D, -NH(C_{1-4} alkyl) substituted with 0-2 R_D, -N(C_{1-4} alkyl)(C_{1-4} alkyl) each independently substituted with 0-2 R_D, -XR_A, and Y;

R_D is independently selected at each occurrence the group consisting of halogen, hydroxy, cyano, C_{1-4}alkyl, -O(C_{1-4}alkyl), -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)(C_{1-4}alkyl), morpholino, pyrrolidino, piperidino, thiomorpholino, piperazino, 4-hydroxypiperidino, -S(O)$_n$(C_{1-4}alkyl), trifluoromethyl, trifluoromethoxy, CO(C_{1-4}alkyl), CONH(C_{1-4}alkyl), CON(C_{1-4}alkyl)(C_{1-4}alkyl), -XR_A, and Y;

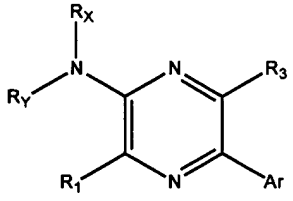
X is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_B-, -O-, -C(=O)-, -C(=O)O-, -S(O)$_n$-, -NH-, -NR_B-, -C(=O)NH-, -C(=O)NR_B-, -S(O)$_n$NH-, -S(O)$_n$$NR_B$-, -OC(=S)S-, -NHC(=O)-, -NR_BC(=O)-, -NHS(O)$_n$-, -OSiH_n(C_{1-4}alkyl)$_{2-n}$-, and –NR_BS(O)$_n$-; and

Y and Z are independently selected at each occurrence from the group consisting of: 3- to 7-membered carbocyclic and heterocyclic groups, which are saturated, unsaturated, or aromatic, which may be substituted with one or more substituents selected from halogen, haloalkyl, oxo, hydroxy, amino, C_{1-4} alkyl, -O(C_{1-4} alkyl), -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), and -S(O)$_n$(C_{1-4} alkyl), and

said 3- to 7-membered heterocyclic groups contain one or more heteroatom(s) selected from N, O, and S, with the point of attachment being either carbon or nitrogen; and

n is independently selected at each occurrence from 0, 1, and 2.

9. (twice amended) A compound of the Formula:



Formula A

wherein:

R_1 is selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halogen, CN, C_{1-4} haloalkyl, trifluoromethyl, trifluoromethoxy, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), -O(C_{1-4} alkyl), and $S(O)_n$(C_{1-4} alkyl);

R_3 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, -O(C_{1-4} alkyl), -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), and -$S(O)_n$(C_{1-4} alkyl), haloalkyl, trifluoromethyl, trifluoromethoxy, $-XR_A$ and Y;

R_X and R_Y are the same or different and are independently selected <u>from</u>[straight, branched, or cyclic alkyl groups having from 1 to 8 carbon atoms, which may contain one or more double or triple bonds, each of which may be further substituted with one or more substituent(s) independently selected from hydroxy, halogen, -O(C_{1-4} alkyl), -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl),]: hydrogen and straight, branched, or cyclic alkyl groups consisting of 1 to 8 carbon atoms, each of which alkyl groups may contain one or more double or triple bonds, and may be further substituted with one or more substituent(s) selected from oxo, hydroxy, halogen, -O(C_{1-4} alkyl), -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), -NHC(O)(C_{1-4} alkyl), -N(C_{1-4} alkyl)C(=O)(C_{1-4} alkyl), -NHS$(O)_n$(C_{1-4} alkyl), -$S(O)_n$(C_{1-4} alkyl), -$S(O)_n$NH(C_{1-4} alkyl), -$S(O)_n$N(C_{1-4} alkyl)(C_{1-4} alkyl), Z, and phenyl, optionally mono-, di- or tri-substituted with substituents independently chosen from C1-4 alkoxy, C1-4 alkyl, halogen, CF[3]<u>3</u>, OCF[3]<u>3</u>, OCHF[2]<u>2</u>, OH, and CN<u>, with the proviso that at least one of R_X or R_Y is not hydrogen;</u> and

Ar is phenyl, mono-, di-, or tri-substituted with R_C, or

Ar is selected from the group consisting of:

naphthyl, pyridyl, pyridonyl, pyrimidinyl, and thiophenyl, each of which is unsubstituted or mono-, di-, or tri-substituted with R_C;

with the proviso that if Ar is phenyl, phenyl substituted with halogen, napthyl, or naphthyl substituted with halogen, then the compounds where R_3 is hydrogen are excluded;

R_A and R_B, which may be the same or different, are independently selected at each occurrence from the group consisting of: hydrogen and straight, branched, or cyclic alkyl groups

consisting of 1 to 8 carbon atoms, which may contain one or more double or triple bonds, each of which may be further substituted with one or more substituent(s) selected from oxo, hydroxy, halogen, -O(C_{1-4} alkyl), -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), -NHC(O)(C_{1-4} alkyl), -N(C_{1-4} alkyl)C(=O)(C_{1-4} alkyl), -NHS(O)$_n$(C_{1-4} alkyl), -S(O)$_n$(C_{1-4} alkyl), -S(O)$_n$NH(C_{1-4} alkyl), -S(O)$_n$N(C_{1-4} alkyl)(C_{1-4} alkyl), and Z;

R_C is independently selected at each occurrence from the group consisting of halogen, cyano, haloalkyl, trifluoromethyl, trifluoromethoxy, hydroxy, amino, and C_{1-6} alkyl optionally substituted with 0-2 R_D, C_{2-6} alkenyl substituted with 0-2 R_D, C_{1-4} alkynyl substituted with 0-2 R_D, C_{3-7} cycloalkyl substituted with 0-2 R_D, (C_{3-7} cycloalkyl)C_{1-4} alkyl substituted with 0-2 R_D, -O(C_{1-4} alkyl) substituted with 0-2 R_D, -NH(C_{1-4} alkyl) substituted with 0-2 R_D, -N(C_{1-4} alkyl)(C_{1-4} alkyl) each independently substituted with 0-2 R_D, -XR_A, and Y;

R_D is independently selected at each occurrence the group consisting of halogen, hydroxy, cyano, C_{1-4}alkyl, -O(C_{1-4}alkyl), -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)(C_{1-4}alkyl), morpholino, pyrrolidino, piperidino, thiomorpholino, piperazino, 4-hydroxypiperidino, -S(O)$_n$(C_{1-4}alkyl), trifluoromethyl, trifluoromethoxy, CO(C_{1-4}alkyl), CONH(C_{1-4}alkyl), CON(C_{1-4}alkyl)(C_{1-4}alkyl), -XR_A, and Y;

X is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_B-, -O-, -C(=O)-, -C(=O)O-, -S(O)$_n$-, -NH-, -NR_B-, -C(=O)NH-, -C(=O)NR_B-, -S(O)$_n$NH-, -S(O)$_n$$NR_B$-, -OC(=S)S-, -NHC(=O)-, -NR_BC(=O)-, -NHS(O)$_n$-, -OSiH_n(C_{1-4}alkyl)$_{2-n}$-, and –NR_BS(O)$_n$-;

Y and Z is independently selected at each occurrence from the group consisting of: 3- to 7-membered carbocyclic and heterocyclic groups, which are saturated, unsaturated, or aromatic, which may be substituted with one or more substituents selected from halogen, haloalkyl, oxo, hydroxy, amino, C_{1-4} alkyl, -O(C_{1-4} alkyl), -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), and -S(O)$_n$(C_{1-4} alkyl), and

said 3- to 7-membered heterocyclic groups contain one or more heteroatom(s) selected from N, O, and S, with the point of attachment being either carbon or nitrogen; and

n is independently selected at each occurrence from 0, 1, and 2.